Remarks

This responds to the Office Action mailed on June 25, 2008.

Claim 1 is amended. Applicant respectfully submits that no new matter was added by way of amendment. Claims 1-14 are pending.

Claim Objections

Claim 3 is objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant respectfully disagrees with this objection. Claim 1 recites, *inter alia*, "...an iscom particle comprising fraction A of Quil A together with *at least on other adjuvant*...." Claim 2 further defines the "*at least one other adjuvant*." Claim 3 further defines the "*at least one other adjuvant*" of claim 2. Thus, contrary to the Examiner's indications, claim 3 does further limit the subject matter of a previous claim. Applicant respectfully requests withdrawal of this rejection.

The 35 U.S.C. § 102 Rejection of the Claims

Claims 1-2, 4-9 and 14 were rejected under 35 U.S.C. § 102(b) for anticipation by Friede et al. (U.S. Patent No. 6,558,670). This rejection is respectfully traversed.

The Examiner states that Friede et al. disclose the adjvuant CpG and that CpG could be administrated in free form or complexed to, for example, an ISCOM. However, Friede et al. further disclose that the adjuvant other than the saponin i.e. the oligonucleotide such as CpG, can only be in free form or associated with the saponin if integrated into the same carrier, such as ISCOM. This is evident from column 9, lines 29-33, and especially from column 9, lines 39-43, where it is stated: "[t]he CpG and saponin in the adjuvants or vaccines of the present invention may be separate or associated. For example, the CpG and saponin may be in free suspension or may be associated via a carrier such as aluminium hydroxide or by a cationic liposome or ISCOM." Clearly they are associated via one and the same carrier. This is especially so with regards to the antigen where it is expressively stated that "[i]n this case, the antigen may be free suspension or associated with a separate carrier" (column 9 lines 37-38). Applicant respectfully

submits that has Friede et al. foreseen different carriers also for the saponin and the other adjuvant (e.g., the oligunucleotide) they would stated such.

Further, the Examiner points out that Friede et al. cite fractions QS21, A7 and QS17. Fraction QS21 is enclosed in fraction C of Quil A and Fraction QS7 is enclosed in fraction A of Quil A used by the present Applicant. However, fraction A and C also contain other saponins than QS7 and QS21 respectively. The Friede et al. ISCOMs however do not contain the full component A of Quil A, but only fraction QS7 of fraction A of Quil A.

Applicant respectively submits that Fraction A of Quil A is non-haemolytic and activates dendritic cells. This activation helps both the antigen and other immune stimulating adjuvants to further activate the immune response. To the contrary, according to Friede et al,. column 5, lines 1-4, QS 7 is haemolytic. This is also stressed in column 12, lines 9-12, where it is stated "[t]aken together, these results show clearly the potential of intranasal formulations combining a lytic saponin and an immunostimulant." Thus, it is submitted that the fraction QS 7 of Friede et al. is not fraction A of Quil A.

Additionally, in Attachment 1, titled "Intranasal administration of PR8 micelles," Applicant has tested fraction A and C from Quil A. It is evident that Fraction A of Quil A does not improve the IgA titre (columns 2, 3 and 4 of the Figure) in *intranasal* administration. This is contrary to the QS21 in Example 1 of Friede et al. Further, fraction A of Quil A is not haemolytic. This is also evident from Cox et al., please see discussion below.

In Attachment 2, titled "Intranasal administration of ovalbumin OVA," Applicant demonstrates the IgG titre after intranasal administration of OVA and different ISCOM matrices (*intranasal* administration of fraction A and C together in the same ISCOM particle and each in different ISCOM particles). It is evident that Fraction A and C in different particles (third column in the Figure) give a lower IgG titre than ISCOM matrix made of mixture of Quil A saponins (2nd column) and fraction A and C in the same ISCOM matrix (4th column) after *intranasal* administration.

Applicant notes that claim 1 has been amended to recite, *inter alia*, "intraperitoneally or subcutaneously administering...." Thus, claim 1 differs from Friede et al. in at least two ways. First, the adjuvants, when integrated into ISCOM or ISCOM matrix are in separate particles. Second, the administration route has been limited so that an intranasal route, which is less

effective for fraction A of Quil A, is no longer within the scope of the claims. Further, it has been shown that these two differences separately bring about a better adjuvant effect.

Thus, Applicant respectfully submits that the instant claims are not anticipated by the cited document. Therefore, Applicant respectfully requests withdrawal of the rejection.

The 35 U.S.C. § 103 Rejection of the Claims

Claims 1, 3 and 10-13 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Friede et al. (U.S. Patent No. 6,558,670) in view of Cox et al. WO 96/11711). This rejection is respectfully traversed.

Friede et al. is discussed above.

Cox et al. relate to a saponin preparation comprising from 50% to 90% by weight of fraction A of *Quillaja Saponaria* and from 50% to 10% by weight of fraction C of Quil A. Even though the document appears to mention an ISCOM matrix, it does not disclose that different types of saponin fractions may be integrated into different ISCOM matrix particles or that this should bring about any advantages.

Cox et al. describe a purification procedure of fractions QHA, QHB and QHC of Quil A, for which the nomenclatures in the instant application are fractions A, B and C. The Cox et al. patent also describes the incorporation of each one of these fractions solitarily into matrix, and the combination of 70% of fraction A and 30 % of C into the same matrix particle (prep 703) i.e. in the same entity, but not to separate the fractions into separate particles.

Cox et al. further describe retained or even enhanced adjuvant properties of 703 ISCOM s or in ISCOM -Matrix formulations compared to what is induced by the same amount of non-fractionated saponin (Quil A) or Fraction-C saponin (prep 0:0:10) alone. Further, the Cox et al. patent describes that these fractions are capable of forming iscoms having optimal adjuvant activity, but minimal haemolytic effects. The haemolytic activity of the 703 mixture is shown to be only marginally lower than that of Fraction-C, which is surprising considering the low haemolytic activity of the Fraction-A component constituting 70% of the mixture. In view of the fact that fraction A is the major part of the 703 preparations such mixtures should be considerably less haemolytic than Quil A and fraction C in ISCOM s or ISCOM - matrix preparations.

Table 1 on page 8 of Cox et al. shows that fraction A has very low haemolytic activity and that fraction C has high haemolytic activity. In Example 7, the haemolytic activity of the combination of 70% of fraction A and 30% of fraction C in the same ISCOM is compared with the haemolytic activity of fraction A and C alone respectively in ISCOM.

Fraction A in ISCOM can be given in more than 800 μg/ml without giving haemolytic activity. Fraction C in ISCOM has haemolytic activity at a concentration of 20 μg/ml. Based on this one would expect a combination of 70% A and 30 % C in the same ISCOM complex to give:

$$\frac{70*800+30*20}{100} = 566\mu g/ml.$$

However, there is a haemolytic activity already at a concentration of 150 μg/ml. Thus, when fraction A and C are mixed in the same particle the haemolytic reaction of C is increased. Furthermore, the Cox et al. patent also discloses that QHA and QHC in the same i.e. 703 matrix particle enhances immunogenicity and that the side effects are acceptable. In spite of this information and claims of the Cox et al. patent, the 703 formulation is abandoned for prophylactic and therapeutic uses due to toxicity.

Thus, Applicant respectfully submits that the instant claims are not rendered obvious by the cited documents. Therefore, Applicant respectfully requests withdrawal of the rejection.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612) 373-6905 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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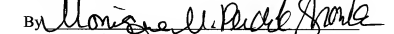
By 
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 27TH day of October 2008.

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